Prevention of Colorectal Neoplasia

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Abstract

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality worldwide. There are well-established screening protocols involving fecal testing, radiographic, and endoscopic evaluations that have led to decreased incidence and mortality of CRC in the United States. In addition to screening for CRC, there is interest in preventing colorectal neoplasia by targeting the signaling pathways that have been identified in the pathway of dysplasia progressing to carcinoma. This review will detail the efficacy of multiple potential preventative strategies including lifestyle changes (physical activity, alcohol use, smoking cessation, and obesity); dietary factors (dietary patterns, calcium, vitamin D, fiber, folate, and antioxidants and micronutrients); and chemopreventive agents (nonsteroidal anti-inflammatory drugs, statins, metformin, bisphosphonates, and postmenopausal hormonal therapy).

Keywords

- chemoprevention
- primary prevention
- colorectal cancer
- adenoma

Colorectal cancer (CRC) is the third most common cancer and cause of cancer mortality among men and women in the United States with an incidence of 50/100,000 and mortality rate of 16.3/100,000.[1] This translates to a 5% lifetime risk of CRC in the United States.[1,2] Both the incidence and mortality of CRC in the United States have been gradually declining over the last decade, which is attributed to improved screening.[1,2] Screening is associated with a 15 to 33% decrease in mortality following a diagnosis of CRC, and colonoscopy with polypectomy is associated with CRC prevention.[3–5] While the improvements in incidence and mortality are encouraging given the high prevalence of CRC, there are still significant strides to be made in primary prevention.

Early epidemiologic studies that analyzed trends in CRC across nationalities and time provided initial evidence of the influence of environmental factors on the incidence of CRC.[6–8] These early studies have driven research focusing on prevention of colorectal neoplasia with lifestyle modifications (e.g., exercise and dietary modification) and pharmacologic or natural agents collectively known as chemoprevention.[9] CRCs are thought to arise from cumulative histologic and molecular changes that eventually result in abnormal regulation of cellular function, cell growth, differentiation, adhesion, and migration.[10] The eventual endpoint of these changes is the transformation of colonic epithelial cells to adenomatous polyps and then into invasive carcinomas.[10,11] With the well-studied sequential stepwise transformation of colorectal neoplasms as discussed in more detail earlier in this issue of *Clinics*, there are multiple targets for chemopreventive agents to stop this progression. It may be assumed that prevention of cancer may also be, at least in part, due to decreasing colorectal polyp formation.

The ideal primary preventative agent must target a step in carcinogenesis, have efficacy, be cost-effective, have easy administration, and have a favorable side effect profile. In this article, we will review a wide host of primary preventative strategies to prevent colorectal adenoma and carcinoma formation.

Lifestyle Modifications

There are several lifestyle modifications with extensive epidemiological evidence that support primary prevention of CRC. As most of these modifiable factors are difficult to effectively randomize, the bulk of the evidence for these factors comes from case–control and cohort studies. In the following sections, we review the effects of exercise, alcohol consumption, smoking cessation, and obesity on CRC prevention.

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Exercise

There is a large amount of observational data that suggest that regular physical activity is associated with protection from CRC.[12–15] Investigators have hypothesized that interactions between insulin-like growth factor-binding proteins (IGFBP), higher vitamin D levels, higher amounts of water intake, anti-inflammatory action, direct immune action, and/or decreased fecal transit time may account for the preventative effect of exercise.[14,16] There have been several systematic reviews and meta-analyses based on observational studies that have evaluated the effect of exercise on CRC. In one review of 21 observational studies that included 17,683 patients with colon cancer, a 26% reduction in the rate of colon cancer among patients who exercised was noted (relative risk [RR] = 0.73, 95% confidence interval [CI]: 0.66–0.81).[17] Another meta-analysis included 52 studies with a very similar 24% reduction in the rate of colon cancer among patients who exercised (RR = 0.76, 95% CI = 0.72–0.81).[16] The exact amount of exercise required to achieve this reduction is unclear, with some studies suggesting walking briskly for 1 to 2 hours per week is enough to result in this reduction while other studies suggest that more exercise is required.[16,18,19] With the well-studied benefits of exercise on the risk of CRC, other cancers, cardiovascular disease (CVD), and overall health, patients should be counseled to pursue an exercise regimen, even if this simply consists of a walking program.[16,17,20]

Alcohol

There is a large amount of observational data that alcohol consumption is related to increased risks of CRC.[21,22] It is estimated that 3.6% of cancers and 3.5% of all cancer deaths worldwide are attributable to alcohol.[23] The exact mechanism of alcohol consumption triggering carcinogenesis is unclear but seems most likely mediated by carcinogenic metabolites such as acetaldehyde, which may directly cause cell injury or gene mutations or indirectly cause decreased glutathione synthesis and free radical formation.[24,25]

Similar to physical activity, there have been several systematic reviews and meta-analyses based on observational trials with a lack of prospective randomized control trials. In one meta-analysis that included 61 studies, a progressive dose–response relationship between alcohol and CRC was found with any drinkers (RR = 1.12, 95% CI = 1.06–1.19); medium drinkers (2–3 drinks/day) (RR = 1.21, 95% CI = 1.13–1.28); and heavy drinkers ($\geq$3 drinks/day) (RR = 1.52, 95% CI = 1.27–1.81).[21] There was no relationship observed between light drinkers ($\leq$1 drink/day) and CRC risk (RR = 1.00, 95% CI = 0.95–1.05).[21] Another meta-analysis that included five cohort studies in Japan with 2,231,010 person-years studied and 2,802 CRC cases demonstrated a similar progressive dose–response relationship of alcohol intake and CRC risk where 23 to 45.9, 46 to 68.9, 69 to 91.9, and $\geq$92 g/day were associated with an RR = 1.42 (95% CI = 1.21–1.66), RR = 1.95 (95% CI = 1.53–2.49), RR = 2.15 (95% CI = 1.74–2.64), and RR = 2.96 (95% CI = 2.27–3.86), respectively.[26] This study also noted that the alcohol–CRC association was stronger among Japanese than in Western populations.[26]

When counseling a patient on the role of alcohol on the primary prevention of CRC, one can state that the current literature points to a direct dose–response relationship with long-term alcohol use and CRC that starts at two drinks per day and increases as the number of drinks per day increases.

Smoking Cessation

Smoking is associated with a host of cancers and health risks, and there is strong observational evidence that smoking is associated with adenomatous polyp formation and CRC incidence and mortality.[27–29] Tobacco and smoking produce a large number of carcinogens that have been shown to directly cause irreversible DNA damage to colorectal mucosa that can initiate the pathway to carcinoma.[30]

There have been several systematic reviews and meta-analyses based on observational studies investigating the relationship between smoking and CRC risk. One of these studies included 42 observational trials consisting of 15,354 cases and 100,011 controls to examine the effect of smoking on the formation of adenomatous polyps. This study found that in comparison with nonsmokers, current smokers (RR = 2.14, 95% CI = 1.86–2.46); former smokers (RR = 1.47, 95% CI = 1.29–1.67); and ever-smokers (RR = 1.82, 95% CI = 1.65–2.00), all had significantly increased risks of adenomas. Furthermore, there was a relationship wherein ever-smokers had a higher rate of high-risk adenomas.[28] Another meta-analysis including 106 observational studies found that ever-smokers had a moderately increased risk of CRC compared with nonsmokers, (RR = 1.18, 95% CI = 1.11–1.25) with a statistically significant dose–response relationship only after 30 years of smoking.[27] This same study also reported a higher risk of CRC mortality among ever-smokers compared with nonsmokers (RR = 1.25, 95% CI = 1.14–1.37).[27]

Thus, while the overall risk of smoking on the rate of CRC is moderate ($\sim$18% higher risk for ever-smokers), patients should be counselled to quit smoking both for their colorectal neoplasia risk in addition to the risks of other cancers and overall health status.

Obesity

The relationship between obesity and CRC has also been assessed in observational studies.[31–33] The exact mechanism of obesity resulting in CRC is not fully understood but likely involves modulation of endogenous hormones such as insulin, insulin-like growth factors, sex steroids, and adipocyte-derived factors (e.g., leptin and adiponectin).[31,33,34]

There have been several systematic reviews and meta-analyses based on observational studies to assess the interaction of obesity and CRC. One of these studies evaluated 30 prospective studies and found a 5-unit increase in BMI corresponded to a 30% increased risk of CRC in men (RR = 1.30, 95% CI = 1.25–1.35) and a 12% increased risk of CRC in women (RR = 1.12, 95% CI = 1.07–1.18).[33] Another meta-analysis included 13 studies and found that the highest BMI category (not explicitly defined) compared with a reference category was associated with an increased risk of colon cancer (hazard ratio [HR] = 1.16, 95% CI = 1.08–1.24).[31]

Interestingly, in this analysis, there was no benefit with each 5 kg of weight loss (HR = 0.96, 95% CI = 0.89–1.05) but some mild harm for each 5 kg of weight gain (HR = 1.03, 95% CI = 1.02–1.05).[31]

The literature does point to an association of obesity and the incidence of CRC. It remains unclear if the association of obesity with colorectal neoplasia is an actual relationship or is confounded by other variables that contribute to CRC risk (e.g., diet, exercise, and alcohol consumption). The literature at this time also suggests that weight loss does not result in improvements in CRC risk.[31] It is reasonable to recommend weight loss for overweight and obese patients for their overall health, but it is unclear if this modulates their risk of CRC at this time.

Dietary Modification and Nutritional Supplements

Epidemiological studies of various geographic dietary patterns' impact on the incidence of CRC have led to several studies to target chemopreventive agents for CRC. Attempts are now being made to better define individual compounds within diets that reduce the risk for CRC to try and identify targeted agents for further study.

Fruits and Vegetables

Increasing intake of fruit and vegetables has been studied in a variety of case–control and cross-sectional studies with some controversy about efficacy.[35–39] The mechanism of this prevention is thought to be multifactorial with effects from micronutrients, dietary fiber, and phytochemicals all interacting to modify colonic inflammation and CRC gene mutations.[40]

There have been a large number of case–control series and some prospective cohort studies to evaluate the effect of fruits and vegetables on CRC risk. In an analysis of 14 cohort studies that included 756,217 men and women followed up for a period of 6 to 20 years, there was no significant difference between the pooled RRs of CRC for the highest- versus lowest-quintile consumption of fruits (RR = 0.91, 95% CI = 0.82–1.01), vegetables (RR = 0.94, 95% CI = 0.86–1.02), and fruits and vegetables combined (RR = 0.90, 95% CI = 0.77–1.05).[35] In the Nurses' Health Study and Health Professional Study including 743,645 total person-years, a difference in fruit and vegetable consumption of one additional serving per day was associated with no change in the rate of CRC (RR = 1.02, 95% CI = 0.98–1.05).[37] Another study that included 19 prospective studies demonstrated an 8% risk reduction for fruit and vegetable use comparing the highest- to the lowest-quintile (RR = 0.92, 95% CI = 0.86–0.99) which was statistically significant.[41] This relationship was not statistically significant for any of the other quintiles of fruit and vegetable intake, which essentially meant that after consuming 100 g of fruit or vegetable per day (the equivalent of a daily apple), there is no further expected reduction in CRC risk.[41,42]

In contrast to simply increasing fruit and vegetable intake, vegetarian dietary patterns and pescovegetarian patterns did demonstrate significant reductions in CRC rates in a trial including 96,354 men and women with a mean follow-up of 7.3 years.[43] In this trial, vegetarians had a 22% lower chance of having CRC as compared with nonvegetarians (RR = 0.78, 95% CI = 0.64–0.95), and pescovegetarians had a 43% lower chance of CRC (RR = 0.57, 95% CI = 0.40–0.82).[43]

Based on these analyses, increasing fruit and vegetable intake may help with other chronic diseases but do not appear to significantly reduce the risk of CRC. An entirely vegetarian or pescovegetarian dietary pattern does appear to mitigate CRC risk.

Red Meats

Diets high in red meat are associated with increased rates of CRC in several large prospective cohort analyses.[44–49] The mechanism felt to drive this interaction is multifactorial with components of direct mutagenic effect of heterocyclic amines after meat is cooked at high temperature and formation of carcinogenic N-nitroso compounds in the gastrointestinal tract.[49]

In a meta-analysis of 21 prospective studies, there was a 22% increased rate of CRC for the highest versus lowest intake of red and processed meats (RR = 1.22, 95% CI = 1.11–1.34), and a 14% increased rate of cancer for each 100 g/day increase in red and processed meats (RR = 1.14, 95% CI = 1.04–1.24).[49] This study then performed a nonlinear dose–response meta-analysis which demonstrated significant increases in the rate of CRC which was first noticed in patient populations eating as low as 20 g of meat daily.[49] This effect plateaued around 140 g/day.[49] There is some data that this effect is modulated by genetic characteristics of individuals.[50]

When reviewing the current literature, the results of these trials point to a mildly increased risk of CRC with red meat consumption. This also corresponds with previously described evidence that vegetarian and pescovegetarian diets reduce the risk of CRC. It is important to note that red meats do have beneficial properties including repletion of vitamin B12 and iron, so counseling patients to limit their red meat intake needs to take this into account.

Dietary Fat

The role of dietary fat patterns and the risk of CRC were initially investigated in epidemiologic-based studies with promising results, but a subsequent randomized controlled trial demonstrated no reduction in risk.[48,51,52] Dietary fat was thought to potentially increase CRC risk via changes in cell membrane structure and subsequent changes in cell signaling and repair mechanisms.[53,54] A large randomized control trial which included 48,835 postmenopausal women demonstrated no benefits with lowering dietary fat consumption on CRC rates.[51] Participants in this study were assigned no dietary modification or intensive behavioral dietary modification counseling designed to support reductions in dietary fat, increased consumption of vegetables and fruit, and increased grain servings which resulted in changes in the intervention arm's dietary patterns.[51] However, this decreased dietary fat intake did not change the rate of CRC (RR = 1.08, 95% CI = 0.90–1.29).[51] Therefore, counseling patients on a balanced diet while minimizing saturated and trans-unsaturated fats is appropriate for their overall health, but it does not appear to impact rates of CRC.

Calcium

The role calcium plays in chemoprevention of CRC has been extensively studied, including three randomized controlled trials and several meta-analyses.[55–58] The mechanism that drives this potential interaction is multifactorial with calcium directly mediating decreased inflammation in response to bacterial flora, calcium-binding secondary bile acids or ionized fatty acids and thus diminishing these substances' carcinogenic properties, and calcium mediating direct reduction of cell proliferation and promotion of cell differentiation perhaps through favorable changes on gene expression in the APC/β-catenin pathway.[57]

There have been discordant results based on systemic reviews, randomized controlled trials, and prospective cohort studies on the role of calcium in colorectal neoplasia.[57] A Cochrane review based on two randomized controlled trials with 1,346 subjects with a recent history of colorectal adenoma followed up for 3 to 4 years demonstrated a 26% decreased rate of development of recurrent adenoma among patients who had calcium supplementation of either 1,200 mg/day for 4 years or 2,000 mg/day for 3 years (OR = 0.74, 95% CI = 0.58–0.95).[55,58,59] Meanwhile, a prospective, randomized, double-blind, placebo-controlled trial involving 36,282 postmenopausal women where women received 1,000 mg of elemental calcium daily and 400 IU of vitamin D3 daily or placebo for 7 years found no significant difference in the rate of CRC formation between placebo and treatment arms (HR = 1.08, 95% CI = 0.86–1.34).[56] A more recent meta-analysis based on prospective nonrandomized observational studies demonstrated a dose–response relationship wherein each 300 mg/day increase in calcium was associated with an 8% reduction risk of CRC (RR = 0.92, 95% CI = 0.89–0.95) from 15 studies with follow-up of 3.3 to 16 years.[57]

With the current available evidence, calcium supplementation is associated with approximately a 26% reduction in adenomatous polyp formation among patients who already have polyps.[60] The optimal dose is unclear, but a dose around 1,200 to 2,000 mg is reasonable for polyp prevention. It is unclear if this will result in CRC prevention in a general patient population.

Vitamin D

Vitamin D has also been studied as a potential chemopreventive agent with a variety of prospective cohort studies and one well-designed randomized controlled trial.[56,61–64] Vitamin D is thought to act via calcitriol to regulate the cell cycle and cell division by improving differentiation while decreasing proliferation, invasiveness, angiogenesis, and metastatic potential.[61,65]

A systematic review and meta-analysis was performed of nine prospective studies and compared various plasma levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D with the rate of CRC.[61] This study found that the highest- versus lowest-quantile of circulating 25-(OH)D levels experienced a 34% decrease in the rate of CRC (OR = 0.66, 95% CI = 0.54–0.81).[61] However, this study also made note that there are seasonal variations in the levels of vitamin D and that patients who exercise and take multivitamins also tended to have higher levels of vitamin D potentially confounding their results.[61] Another prospective, randomized, double-blind, placebo-controlled trial involving 36,282 postmenopausal women where women received 1,000 mg of elemental calcium daily and 400 IU of vitamin D3 daily or placebo for 7 years found no significant difference in the rate of CRC development between placebo and treatment arms (HR = 1.08, 95% CI = 0.86–1.34).[56] Experts who criticized this study felt that a higher level of vitamin D3 supplementation is required (1,000 IU daily felt to be needed) to see an effect on CRC rates and that longer follow-up was needed to see a change.[64]

Currently, there is not enough evidence to recommend for or against vitamin D supplementation to reduce the risk of CRC. Future randomized trials should include higher levels of vitamin D supplementation.

Fiber

Dietary fiber is another agent studied as a possible means to decrease CRC incidence. Burkitt noted in the early 1970s that CRC was rare in rural Africa compared with industrial countries, which he proposed was due to dietary fiber.[7] Proposed mechanisms for a protective effect include increasing stool bulk, decreasing colonic transit time (thus decreasing contact time with carcinogens), binding bile acids and carcinogens, decreasing colonic pH, and increasing the production of short chain fatty acids.[66]

There have been many prospective studies and even several randomized or quasi-randomized controlled trials to investigate the use of fiber to decrease colorectal adenomas and carcinomas.[58,67–69] A Cochrane review including five randomized or quasi-randomized studies of patients with a history of adenoma who were randomized to high fiber interventions versus control found no significant differences in the detection of at least one adenoma (RR = 1.04, 95% CI = 0.95–1.13) or more than one adenoma (RR = 0.94, 95% CI = 0.77–1.15) 2 to 4 years after intervention.[67] Another prospective study that utilized the Nurse's Health Study and the Health Professionals Follow-up Study that included 1.8 million person-years found no protective effect of fiber on the rate of CRC when adjusting for confounding variables (RR = 0.99, 95% CI = 0.95–1.04).[70] Thus, based on current prospective evidence, fiber does not appear to have an impact on colorectal adenoma or carcinoma formation.

Folate

Folate and folic acid received a great deal of attention when several epidemiologic studies found a relationship between their use and decreased CRC rates.[71] The mechanism of action of folate supplementation reducing risk of CRC stems from deficiencies in folate resulting in differences in DNA methylation and inappropriate activation of proto-oncogenes and therefore resulting in potential malignant transformation.[72]

Similar to fiber, initial promising epidemiologic and retrospective studies of the efficacy of folate have not been substantiated by prospective trials. In a well-performed meta-analysis of six randomized trials comparing folic acid versus placebo, there was no difference in the rate of colorectal adenoma among patients who had a personal history of adenoma (RR = 0.93, 95% CI = 0.61–1.41).[73] There was also

no difference noted in the rate of CRC in a general population in patients who took folic acid versus placebo (RR = 1.13, 95% CI = 0.77–1.64).[73] In another well-designed randomized controlled trial, folic acid was associated with higher risks of having three or more adenomas and of non-CRCs.[74] This study raised the possibility that folic acid supplementation might paradoxically increase cancer occurrence in select patients.[74]

In summary, there is good evidence that folic acid and/or folate does not decrease the rate of colorectal adenoma or carcinoma and may paradoxically increase the risk of colorectal adenomas in select patients.

Antioxidants and Micronutrients

Based on epidemiologic data on the role fruits and vegetables play in the development of CRC, there has been a large body of research on individual components in fruits and vegetables that might drive CRC prevention. There are a large number of studied compounds including phytochemicals, various vitamins (A, B6, B12, C, D, E), flavonoids, resveratrol, selenium, garlic, magnesium, ginger, curcumin, and others. A complete discussion of all of these compounds is beyond the scope of this review. In general, while case–control and cohort series have at times been promising for beneficial effects for the bulk of these substances, further investigation with prospective randomized trials has demonstrated a lack of evidence that they prevent colorectal adenoma or carcinomas.[42,75–77] There are ongoing investigations into many of these compounds including in vitro and in vivo modeling that may provide more targeted chemotherapeutics in the future.

Chemoprevention

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most studied chemopreventive agents for CRC. There are several proposed mechanisms through which NSAIDs cause decreased rates of CRC. Most of these mechanisms are driven by two interactions: NSAIDs induce apoptosis, and cyclooxygenase and inflammation (both of which NSAIDs inhibit) are involved in colonic tumorigenesis.[78,79]

Aspirin

A recently released draft from the United States Preventive Task Force (USPTF) on aspirin gives a grade B recommendation for low-dose aspirin use in adults aged 50 to 59 years for primary prevention of CVD and CRC who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin for 10 years.[80] For patients aged 60 to 69 years, there is a grade C recommendation to individualize the decision as to whether or not to use aspirin.[80] For patients younger than 50 years and older than 70 years, the USPTF felt there was not enough information to make a recommendation.[80] Aspirin thus represents the first chemopreventive agent for CRC that is preliminarily being recommended for a general population.

The efficacy of aspirin in preventing colorectal adenoma and carcinoma progression has been investigated in several randomized controlled trials and systemic reviews and meta-analyses.[78,81–89] A meta-analysis that included five randomized controlled trials showed that regular use of aspirin reduced the incidence of colonic adenomas by 18% (RR = 0.82, 95% CI = 0.7–0.95).[90] Another meta-analysis that included two large randomized trials with follow-up for more than 20 years demonstrated that the use of aspirin at a dose over 300 mg/day was associated with a 26% reduction in the incidence of CRC after a latency of 10 years (HR = 0.74, 95% CI = 0.56–0.97).[84] This study also noted that the use of less than 300 mg/day of aspirin did not cause a reduction in the rate of CRC.[84] Another meta-analysis that included four prospective, randomized, placebo-controlled trials with doses of aspirin that ranged from 81 to 325 mg/day noted a 17% reduced risk of adenoma (RR = 0.83, 95% CI = 0.72–0.96) and a 28% reduced risk for any advanced lesion (RR = 0.72, 95% CI = 0.57–0.90).[86] This review did not find a difference between higher (>160 mg/day) and lower (<160 mg/day) dose aspirin regimens and the rate of CRC.[86]

Thus, based on high-quality evidence, aspirin does reduce the risk of colorectal adenoma and carcinoma. However, the lowest possible aspirin dose to result in reduced colorectal neoplasia risk is unclear.

The benefit of aspirin in reducing the rate of colorectal neoplasia has to be balanced with its risks (e.g., intestinal bleeding and hemorrhagic strokes).[80] In a systematic review and meta-analysis of low-dose aspirin (50–325 mg/day), the pooled risk of major intestinal bleeding (required transfusion or hospitalization) increased significantly by 59% (odds ratio [OR] = 1.59, 95% CI = 1.32–1.91) and hemorrhagic strokes increased by 33% (OR = 1.33 95% CI = 1.03–1.71).[91] Thus, while there are clear benefits, there are also clear harms.

The association of aspirin and the human genome has also been evaluated to see if aspirin use can be targeted to specific populations who are likely to benefit from it the most. A large prospective study found that NSAID use was associated with lower risk of CRC, but this risk varied according to genetic variation at two single nucleotide polymorphisms at chromosomes 12 and 15.[92] With these results and ongoing research, the future will likely be targeting aspirin use to populations who are more likely to achieve benefit (both in terms of CVD and CRC) and less likely to experience side effects.

For now, the USPTF draft recommendations seem reasonable in recommending low-dose aspirin use in adults aged 50 to 59 years for primary prevention of CVD and CRC who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin for 10 years, and individualizing recommendations in other populations.[80]

Cyclooxygenase-2 Inhibitors

Cyclooxagenase-2 inhibitors (COX-2 inhibitors), including rofecoxib and celecoxib, have been intensely studied for CRC prevention given their decreased risk of intestinal bleeding compared with aspirin with potential similar efficacy in colorectal neoplasia prevention. In one randomized

controlled trial, 1,435 patients with a history of adenoma were assigned to placebo, 200 mg, or 400 mg of celecoxib twice daily.[93] At 3-year follow-up, there was a 33% reduction in adenomas in the lower dose celecoxib group (RR = 0.67, 95% CI = 0.59–0.77) and a 45% reduction in adenomas in the higher dose celecoxib group (RR = 0.55, 95% CI = 0.48–0.64).[93] Unfortunately, celecoxib at both dose ranges was associated with a significantly higher risk of cardiovascular events which caused the investigators to conclude that celecoxib could not be routinely recommended for prevention of colorectal adenomas.[93] Similarly, a randomized controlled trial with rofecoxib demonstrated decreased colorectal adenoma rates but increased rates of cardiovascular events.[94]

Subsequent analyses have shown that celecoxib is likely safe in patients with low-risk of CVD (either based on clinical parameters or on low high-sensitivity C-reactive protein levels).[95,96] However, in light of moderate benefit in colorectal adenoma prevention and serious risk of cardiovascular morbidity, no society has endorsed COX-2 inhibitors for prevention of colorectal neoplasia.

Sulindac

Sulindac, another NSAID, has also been studied in a controlled trial that randomized 375 individuals with a history of adenoma to sulindac and ornithine decarboxylase inhibitor difluoromethylornithine (DFMO) or placebo.[97] This study demonstrated a 70% reduction in the rate of adenomas (RR = 0.30, 95% CI = 0.18–0.49) and a nonsignificant increase in adverse events.[97,98] However, use of this combination has not been widely adopted due to concern of hearing loss and cardiovascular toxicity.[42] Further studies on DFMO in combination with other chemopreventive strategies are warranted.[99]

Statins

Several observational studies demonstrated that statins lowered the risk of CRC.[100–102] The mechanism influencing tumorigenesis is not well understood but is thought to result from anti-inflammatory processes, inhibition of cholesterol synthesis (which may help cell signaling for apoptosis), and other possible apoptotic mechanisms.[103]

Several randomized controlled trials that investigate the efficacy of statins have included the incidence of CRC as secondary endpoints in their analysis. A recent systematic review and meta-analysis of 40 studies including 8 randomized controlled trials, 13 cohort studies, and 19 case–control studies involving more than 8 million subjects demonstrated a nonsignificant reduction in the risk of CRC with statin use within the randomized controlled trials (RR = 0.89, 95% CI = 0.74–1.07) but a marginal, yet statistically significant, effect in the cohort studies (RR = 0.91, 95% CI = 0.83–1.00) and case–control studies (RR = 0.92, 95% CI = 0.87–0.98). Statins do have a significant side-effect profile, including myopathy, hepatotoxicity, and strokes.

With the current level of evidence, statins by themselves may contribute a very modest risk reduction for CRC. In light of significant side effects and cost, statins are not recommended for use solely for CRC prevention.

Metformin

Similar to statins, the role of metformin in CRC has been investigated as a secondary endpoint in several studies.[104–109] The mechanisms of this action are still poorly defined but are theorized to act via modulations in glucose, insulin, insulin-like growth factor 1, IGFBP, and leptin eventually resulting in decreased cell growth and proliferation.[104]

There have been several systematic reviews of the role of metformin on the risk of CRC. In one review with 12 randomized controlled trials and 41 observational studies, metformin had no effect on the rate of CRC in the randomized controlled trials (RR = 1.02, 95% CI = 0.41–2.5) but a slight reduction in observational studies (RR = 0.83, 95% CI = 0.74–0.92).[109] In light of the lack of effect in randomized trials and potential toxicity, metformin is not recommended solely for colorectal neoplasia prevention.

Bisphosphonates

The efficacy of bisphosphonate use and cancers has been investigated in several observational studies.[110–112] Bisphosphonates are proposed to work through inhibition of protein prenylation that eventually results in promotion of apoptosis and inhibition of angiogenesis and tumor cell adhesion.[113] The impact of bisphosphonates on CRC was evaluated in a systematic review and meta-analysis of three case–control and one cohort study which demonstrated a 13% reduction in the rate of CRC (OR = 0.87, 95% CI = 0.78–0.97).[110] However, this study has been widely criticized, as it excluded a large, prospective null study using the Nurses' Health Study which showed that there was a nonsignificant 3% adjusted reduction in CRC after 5 years of use (RR = 0.97, 95% CI = 0.60–1.56).[112] With a lack of prospective randomized data and inconclusive observational data, the role of bisphosphonate therapy in colorectal neoplasia prevention is unclear.

Postmenopausal Hormone Replacement Therapy

Postmenopausal hormone replacement therapy (HRT) was found to reduce the risk of CRC in several epidemiological studies.[114–116] There are several proposed mechanisms including a reduction in methylation of a DNA mismatch repair gene and a potential induction of apoptosis via estrogen receptors.[117] In a large randomized control trial with 16,608 postmenopausal women between 50 and 79 years of age that compared estrogen plus medroxyprogesterone versus placebo, a 44% reduction in the overall number of CRCs was found in the treatment arm (RR = 0.56, 95% CI = 0.38–0.81).[116] However, patients in the HRT group who developed CRC had a higher rate of positive lymph nodes, a higher stage, and a nonsignificant higher number of CRC deaths.[118] Thus, any potential gains with lower rates of CRC diagnoses were mitigated by the more advanced stage at diagnosis among patients taking HRT. The reason for this association is not entirely clear. HRT is also associated with an increased risk of breast cancer, venous thromboembolism, coronary artery disease, stroke, and cholecystitis.[115] Owing to these findings, postmenopausal HRT is not recommended for the prevention of CRC.

Conclusion

There is a large body of literature devoted to finding agents and lifestyle changes that decrease the risk of colorectal neoplasia. In general, a healthy lifestyle (exercising, minimal alcohol consumption, smoking cessation, healthy diet, low red meat intake) is associated with decreased CRC (and likely decreased polyp formation or progression of polyps to cancer) along with improvements in other arenas of health. Multiple chemopreventive agents have been studied with variable results as detailed in ►**Table 1**. Based on current evidence, it is reasonable to recommend calcium supplementation to prevent adenoma formation in patients with a personal history of adenoma, although it is unclear if this will decrease their risk of CRC. A recent draft by the USPTF also recommends aspirin for CRC prevention in a specific patient population. As we further our understanding of the complex interplay between the human genome, the fecal microbiome,

Table 1 Different interventions with risk reductions for colorectal neoplasia

Intervention	Risk reduction for CRC (RR with 95% CI)	Recommendation
Exercise	0.76 (0.72–0.81)[16]	Perform regular physical activity for overall health and colorectal neoplasia prevention
Alcohol use: heavy drinking vs. none	1.52 (1.27–1.81)[21]	Limit regular alcohol intake to $\leq$1 drink/day for overall health and colorectal neoplasia prevention
Smoking	1.18 (1.11–1.25)[27]	Council on smoking cessation for overall health and colorectal neoplasia prevention
Weight loss (per 5 kg lost)	0.96 (0.89–1.05)[31]	Weight loss likely does not change CRC risk. Reasonable to council on weight loss for overall health
Fruit and vegetable intake (one additional serving a day)	1.02 (0.98–1.05)[37]	Increasing fruit and vegetable intake likely does not change CRC risk. Reasonable to council on weight loss for overall health
Vegetarian diet	0.78 (0.64–0.95)[43]	Vegetarian diet and pescovegetarian diet appear to decrease CRC risk
Red meats	1.22 (1.11–1.34)[49]	Reduction of red meats is associated with moderate reduction in colorectal neoplasia. Need supplementation of iron and vitamin B12
Dietary fats	1.08 (0.90–1.29)[51]	Reduction in dietary fats does not change CRC risk. Reasonable to council for overall health
Calcium	Adenoma: 0.74 (0.58–0.95)[55] Carcinoma: 1.08 (0.86–1.34)[56]	Recommend in patients with personal history of polyps (1,200–2,000 mg/day). Unclear if prevents carcinoma
Vitamin D	1.08 (0.86–1.34)[56]	Vitamin D supplementation does not modulate risks of CRC
Fiber	0.99 (0.95–1.04)[70]	Fiber supplementation does not modulate risks of CRC
Folic acid	1.13 (0.77–1.64)[73]	Folic acid supplementation does not modulate risks of CRC
Aspirin	Adenoma: 0.83 (0.72–0.96)[86] Carcinoma: 0.74 (0.56–0.97)[84]	Recommend low-dose aspirin use in adults aged 50–59 years for primary prevention of CVD and CRC who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin for 10 years. Otherwise individualize recommendations[80]
COX-2 inhibitor	Adenoma: 0.67 (0.59–0.77)[93]	Good data on efficacy for colorectal adenoma prevention, but carries increased risks of cardiovascular morbidity. Not recommended at this time for routine use
Statins	0.89 (0.74–1.07)[100]	Marginal if any efficacy with considerable side effects. Not recommended solely for CRC prevention
Metformin	1.02 (0.41–2.5)[109]	Likely not efficacious for CRC prevention. Not recommended solely for CRC prevention
Bisphosphonates	0.97 (0.60–1.56)[112]	Conflicting studies on efficacy for colorectal neoplasia prevention. No prospective randomized data. Not recommended solely for CRC prevention
Postmenopausal hormone therapy	0.56 (0.38–0.81)[116]	Reduction in overall incidence of CRC but no difference in CRC mortality. Also associated with significant adverse events. Not recommended for CRC prevention

Abbreviations: CRC, colorectal cancer; CVD, cardiovascular disease.

and additional therapeutics, more individualized recommendations about specific agents and combinations of agents to prevent colorectal neoplasia will be made to maximize benefit while minimizing side effects. All patients should be encouraged to continue appropriate screening in addition to any chosen lifestyle, dietary, and/or chemopreventive agent(s).

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